REMARKS

I. Status Summary

Claims 1-3, 5-7, 9, 12-15, 17-23, 26-28, 30-33, 35, and 36 are pending and have been examined by the United States Patent and Trademark Office (hereinafter the "Patent Office") in a Final Official Action dated November 17, 2008.

The Abstract has been objected to upon the contention that a clean copy of the amended Abstract was not presented apart from the other text with the previous response.

Claim 15 is newly rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the amendment presented in the previous response introduced new matter.

Claims 1-3, 5-7, 9, 12-15, 17-22, 26, 27, 35, and 36 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Lieber *et al.*, 1999 (73 *J Virol* 9314-9324 (hereinafter "Lieber") in view of U.S. Patent No. 6,383,794 to Mountz *et al.* (hereinafter "Mountz"). Claims 1 and 21-23 have also been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Lieber in view of Mountz and further in view of U.S. Patent Application Publication No. 2003/0017139 of Souza *et al.* (hereinafter "Souza"). Claims 1, 26-28, and 30-33 have also been rejected under this section upon the contention that the claims are unpatentable over Lieber in view of Mountz, and further in view of U.S. Patent No. 5,962,313 to Podsakoff *et al.* (hereinafter "Podsakoff").

Claims 12-15 have been canceled without prejudice. Applicants respectfully reserve the right to file one or more divisional and/or continuing applications with claims directed to the subject matter of the canceled claims.

Claims 2 and 7 have been amended. The amendment to claim 2 is to add a period at the end of the claim. The amendment to claim 7 is to correct a misspelling of the term "metallothionein". Thus, no new matter has been added by the amendments to the claims.

New claims 143-148 have been added. Support for the new claims can be found throughout the specification as filed, including particularly in the original claims (*see e.g.*, original claims 1, 11, 35, and 36). Additional support can be found on page 21, lines 4-10 of the instant specification as filed. Accordingly, no new matter has been added by the inclusion of the new claims.

Reconsideration of the application as amended and based on the remarks presented hereinbelow in view of the Request for Continued Examination submitted herewith is

respectfully requested.

II. Response to the Objection to the Abstract

The Abstract has been objected to upon the contention that the previous amendment to the Abstract presented August 22, 2008 did not include a clean version of the Abstract on a separate sheet apart from any other text. Thus, the Patent Office asserts that the replacement Abstract submitted at that time did not comply with 37 C.F.R. 1.52(b)(4).

Applicants respectfully disagree. Applicants respectfully submit that beginning July 30, 2003, Revised Amendment Practice has been in effect. The REVISED AMENDMENT PRACTICE: 37 CFR 1.121 CHANGED flyer provided by the Patent Office stated in part the following:

> "Amendments to the specification, including the abstract, must be made by presenting a replacement paragraph or section or abstract marked up to show changes made relative to the immediate prior version. An accompanying clean version is not required and should not be presented. Newly added paragraphs or sections, including a new abstract (instead of a replacement abstract), must not be underlined. A replacement or new abstract must be submitted on a separate sheet, 37 CFR 1.72.

REVISED AMENDMENT PRACTICE: 37 CFR 1.121 CHANGED, page 2, section B (emphases added).

Applicants respectfully submit that page 2 of the Amendment filed August 22, 2008 includes the amendments to the abstract, which were presented in a marked up version to show changed made relative to the immediate prior version, and a clean version was not presented as per the REVISED AMENDMENT PRACTICE: 37 CFR 1.121 CHANGED flyer. It is noted additionally that the amended Abstract was presented on a separate page from all other amendments.

Nonetheless, in an effort to facilitate prosecution, applicants have attached hereto on a separate sheet a clean version of a Replacement Abstract that is identical to the Abstract as amended on August 22, 2008. Thus, no new matter has been added by the submission of the Replacement Abstract. Applicants respectfully request that the Patent Office replace the Abstract as filed with the Replacement Abstract submitted herewith.

III. Response to the New Matter Rejection

Claim 15 is newly rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the amendment presented in the previous response introduced new matter. According to the Patent Office, the element "and further wherein the helper cell provides AAV Rep and Cap" added to claim 15 in the amendment presented August 22, 2008, in conjunction with the helper cell with the ability to complement deletions in the adenovirus vector genome is not supported by the specification's disclosure. The Patent Office contends that the newly introduced element reads on a helper or packaging cell that simultaneously provides for both adenovirus vector and AAV vector viral replication and packaging, and further that the specification as filed, while providing for 293 cells transfected with plasmids containing the AAV rep and cap genes, is silent in its disclosure of the claimed helper cells that simultaneously provides for both adenovirus vector and AAV vector viral replication. The Patent Office asserts that at the time the application was filed, one of ordinary skill in the art would not recognize from the disclosure that applicants were in possession of a helper cell that complements deletions in the adenovirus vector genome, and further provides AAV Rep and Cap, as claimed.

In an effort to facilitate prosecution and without acquiescing to the Patent Office's assertions or surrendering any subject matter, applicants have canceled claim 15 without prejudice. Accordingly, applicants respectfully submit that the instant rejection of claim 15 under 35 U.S.C. § 112, first paragraph, has been rendered moot. Applicants respectfully request that it be withdrawn at this time.

IV. Responses to the Rejections under 35 U.S.C. § 103

Claims 1-3, 5-7, 9, 12-15, 17-22, 26, 27, 35, and 36 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Lieber in view of Mountz. Claims 1 and 21-23 have also been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Lieber in view of Mountz and further in view of Souza. Claims 1, 26-28, and 30-33 have also been rejected under this section upon the contention that the claims are unpatentable over Lieber in view of Mountz, and further in view of Podsakoff.

After careful consideration of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

IV.A. Response to the Rejection over Lieber *in view of* Mountz

Claims 1-3, 5-7, 9, 12-15, 17-22, 26, 27, 35, and 36 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Lieber in view of Mountz. According to the Patent Office, Lieber describes integrating adenovirus-AAV hybrid vectors devoid of all viral genes, ITRs inserted into adenovirus (Ad) vector genomes resulting in vector genomes devoid of all viral genes, AAV ITRs flanking a reporter gene cassette inserted into the E1 region; Ad.AAV vector genomes contain only the transgene flanked by AAV ITRs, and packaging signals, and an Ad.AAV2 hybrid vector comprising a neo gene under the control of the SV40 and Tn5 promoters . The Patent Office further contends that as the hybrid vector genome does not include coding sequence for any adenoviral or AAV proteins, it necessarily comprises deletions of the adenovirus polymerase and preterminal protein regions and does not encode AAV Rep or AAV capsid proteins.

The Patent Office concedes, however, that Lieber does not describe their hybrid virus as comprising a functional E4orf6 region. This deficiency is asserted to be cured by Mountz, which the Patent Office contends discloses high titer recombinant AAV hybrid vectors encoding a therapeutic gene flanked by ITRs of AAV and the AAV rep and cap genes, the construction of the hybrid Ad-AAV vector, by cloning the 4.2 kb Xba fragment fragment of AAV pSub201 containing the AAV rep and cap genes into the E1 Xba site of an adenoviral shuttle vector. Thus, the Patent Office contends that it would have been *prima facie* obvious for a person of ordinary skill in the art to combine their respective teachings and to include a functional adenovirus E4orf6 region in the hybrid vector of Lieber, with a reasonable expectation of success, at the time of the instant invention. The Patent Office further asserts that a person of skill in the art would construct such a hybrid adeno/AAV vector as a matter of design choice, which amounts to combining prior art elements according to known methods to yield predictable results.

Applicants respectfully traverse the Patent Office's assertion that Lieber and Mountz support a *prima facie* case of obviousness of the instant claims. Particularly, applicants respectfully submit that contrary to the Patent Office's assertion, Lieber and Mountz are not combinable because the goal in Lieber is to produce an Ad-AAV hybrid vector devoid of all viral genes, and thus one of ordinary skill in the art would not look to Mountz to "add back" any viral genes.

To elaborate, the Patent Office concedes that Lieber describes integrating adenovirus-AAV hybrid vectors devoid of all viral genes on page 6 of the Final Official Action. The deletion of all viral genes is the central goal of the Lieber reference, which states "this hybrid vector should be devoid of all Ad genes whose expression may cause immunological or toxic side effects" (*see* Lieber, paragraph bridging pages 9314-9315). As a result, applicants respectfully submit that Lieber teaches against a vector comprising a functional E4orf6 region as set forth in the instant claims. Thus, and contrary to the Patent Office's assertion, one of ordinary skill in the art would not have looked to Mountz to add these viral regions to the vectors disclosed in Lieber.

Additionally, the Patent Office's assertion that a person of skill in the art would construct such a hybrid adeno/AAV vector as a matter of design choice does not support the instant rejection. It is noted that this assertion amounts to no more than an assertion that obviousness can be established merely by pointing out that the elements of a claim were known in the prior art. However, an obviousness rejection based solely on this minimal showing is specifically proscribed by the U.S. Supreme Court in the *KSR* case. Particularly, *KSR* stands for the proposition that "A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art" (*KSR v. Teleflex*. 127 S.Ct. 1727, 1731). The Supreme Court also stressed that "inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known" (*KSR v. Teleflex*. 127 S.Ct. 1727, 1741). Thus, applicants respectfully submit that the Patent Office"s showing with respect to the instant rejection is insufficient to establish a *prima facie* case of obviousness.

Summarily, the instantly claimed subject matter relates *inter alia* to hybrid Ad-AAV viruses that lack pol and/or pTP. The hybrid viruses are designed to replicate in a helper cell that provides pol and/or pTP, wherein they are packaged into an Ad capsid. A hybrid virus encapsidated in an Ad capsid is then used to infect a helper cell line that expresses rep and cap in order to produce an AAV virus encoding a heterologous gene. Applicants respectfully submit that the combination of Lieber and Mountz does not disclose or suggest such a hybrid virus.

Accordingly, applicants respectfully submit that the combination of Lieber and Mountz do not support a *prima facie* case of obviousness of claim 1. Claims 12-15 have

been canceled, and thus the instant rejection is moot as to these claims. Claims 2, 3, 5-7, 9, 17-22, 26, 27, 35, and 36 all depend directly or indirectly from claim 1, and thus are also believed to be distinguished over the cited combination. As a result, applicants respectfully request that that the instant rejection of claims 1-3, 5-7, 9, 17-22, 26, 27, 35, and 36 be withdrawn at this time.

IV.B. Response to the Rejection over Lieber *in view of* Mountz *and further in view of* Souza

Claims 1 and 21-23 have also been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Lieber in view of Mountz and further in view of Souza. The Patent Office concedes that Lieber and Mountz do not describe their hybrid AAV vectors encoding a heterologous nucleic acid as operatively associated with a liver-specific promoter. However, the Patent Office asserts that Souza describes adeno-associated viral vectors comprising liver specific enhancer/promoter combinations linked to a transgene administered to recipient.

Applicants respectfully traverse the Patent Office's assertion that Lieber in view of Mountz and further in view of Souza supports a *prima facie* case of obviousness of claim 1. Particularly, applicants respectfully submit that Souza does not cure the deficiencies cited hereinabove with respect to the combination of Lieber in view of Mountz.

Summarily, applicants respectfully submit that Lieber in view of Mountz fails to disclose or suggest a hybrid virus that comprises Ad E4orf6 as well as a deletion of pol and/or pTP. At best, Souza discloses AAV vectors that employ different tissue-specific promoters and enhancers. However, applicants respectfully submit that Souza does not disclose or suggest a vector that encodes E4orf6, thus failing to cure the deficiency of Lieber in view of Mountz discussed hereinabove.

Therefore, applicants respectfully submit that the combination of Lieber in view of Mountz and further in view of Souza fails to support a *prima facie* case of obviousness of claim 1. Claims 21-23 all depend directly or indirectly from claim 1, and thus are also believed to be distinguished over the cited combination. As a result, applicants respectfully request that that the instant rejection of claims 1 and 21-23 be withdrawn at this time.

IV.C. Response to the Rejection over Lieber *in view of* Mountz *and further in view of* Podsakoff

Claims 1, 26-28, and 30-33 have also been rejected under this section upon the

contention that the claims are unpatentable over Lieber in view of Mountz, and further in view of Podsakoff. According to the Patent Office, Podsakoff describes an AAV vector comprising a gene encoding a lysosomal enzyme.

Applicants respectfully traverse the Patent Office's assertion that Lieber in view of Mountz and further in view of Podsakoff supports a *prima facie* case of obviousness of claim 1. Particularly, applicants respectfully submit that as was the case with the immediate previous rejection, Podsakoff does not cure the deficiencies cited hereinabove with respect to the combination of Lieber in view of Mountz. Particularly, applicants respectfully submit that Lieber in view of Mountz fails to disclose or suggest a hybrid virus that comprises Ad E4orf6 as well as a deletion of pol and/or pTP. At best, Podsakoff discloses AAV vectors that encode a lysosomal enzyme. However, applicants respectfully submit that Podsakoff does not disclose or suggest a vector that encodes E4orf6, thus failing to cure the deficiency of Lieber in view of Mountz discussed hereinabove.

Therefore, applicants respectfully submit that the combination of Lieber in view of Mountz and further in view of Podsakoff fails to support a *prima facie* case of obviousness of claim 1. Claims 26-28 and 30-33 all depend directly or indirectly from claim 1, and thus are also believed to be distinguished over the cited combination. As a result, applicants respectfully request that that the instant rejection of claims 1, 26-28, and 21-23 be withdrawn at this time.

V. Discussion of the New Claims

New claims 143-148 have been added. Support for the new claims can be found throughout the specification as filed, including particularly in the original claims (*see e.g.*, original claims 1, 11, 35, and 36). Additional support can be found on page 21, lines 4-10 of the instant specification as filed. Accordingly, no new matter has been added by the inclusion of the new claims.

Applicants respectfully submit that new claims 143-148 are believed to be distinguished over the references cited by the Patent Office in the Final Official Action for at least the reasons set forth hereinabove.

Additionally, claims 143-148 recite *inter alia* recombinant hybrid viruses comprising a functional E1a region, recombinant cells stably modified to express a functional pol polypeptide, a functional pTP polypeptide, or both comprising the disclosed recombinant

hybrid viruses, hybrid virus particles comprising the disclosed recombinant hybrid viruses encapsidated within an adenovirus capsid, and adeno-associated virus (AAV) particles produced by introducing the disclosed hybrid virus particles into a cell that expresses AAV Rep and AAV Cap. Applicants respectfully submit that the combination of Lieber and Mountz does not teach or suggest a hybrid virus that contains E1a and a heterologous nucleic acid that is functional. Applicants respectfully submit that Lieber does not teach any hybrid viruses that comprise a functional E1a region. Applicants further respectfully submit that while Mountz does disclose $E1a^+$ hybrid viruses, these viruses would have been recognized by one of ordinary skill in the art to be non-functional.

Specifically, the only $E1a^+$ hybrid viruses disclosed in Mountz also encode functional rep and cap polypeptides. As was known in the art as of the filing date of the instant application, the presence of both rep and E1 in the same cell ultimately results in the death of the cell. This fact is demonstrated by a publication from Dr. Mountz's group itself: Zhang *et al.*, 2001, a copy of which is being submitted herewith as **Exhibit A**. On page 706, **Exhibit A** explicitly states: "AAV Rep inhibits adenovirus replication". This reference also discloses that "upon extended passage of the rAdAAVrep-cap chimeric vector [in 293 cells], a portion of the rep gene is deleted" (*see* page 707), indicating that the presence of rep in an $E1a^+$ 293 cell results in a selection against the rep coding sequences.

Accordingly, applicants respectfully submit that claims 1-3, 5-7, 9, 17-23, 26-28, 30-33, 35, 36, and 143-148 are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

CONCLUSIONS

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account Number **50-0426**.

Respectfully submitted,

JENKINS, WILSON, TAYLOR & HUNT, P.A.

Date: May 18, 2009 By: _____

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Enclosures: Clean Version of Abstract on a Separate Sheet
Exhibit A